Comment on

You receive herewith my comment on the above revision and I would be grateful if you considered it for further discussions and hopefully improvements of the revision and the CTD.

I am prepared to contribute further to the process, e.g. by adhering to respective meetings.

Kind regards

(Schnuch)
Comment on


This comment has the following outline

1. Key issues
2. Explanation of the key issues
3. Comments on the concept paper with focus on 1 and 2
4. Comments on the ‘Roadmap’
5. Conclusions
6. Suggestions
7. stakeholder status
8. Annex (Publication as example for ‘status quo ante’)

I. Key issues

The CTD has as objective “to protect clinical trial subjects”, their “rights, safety and well being” (article 1 (2)).

In the same time the CTD resulted in a substantial weakening in the protection of consumers and workers, putting at risk their safety and health. This unfortunate situation was neither addressed in the CTD and nor in the concept paper for the revision of the CTD. Suggestions in the concept paper may be suitable to improve the situation only to a minor degree.

Although "significant impacts" were discussed (Roadmap for the proposal for a revision of the Directive (Version 3, 04/10/2010), the substantial impact of the Directive on consumers' and workers' safety and health was not considered at all.

II. Explanations

The certainly undesired effect of the CTD further explained below is probably the result of neglecting one particular disease, namely, contact allergy, which is nevertheless one of the most important diseases caused by consumer goods and working materials.

Contact Allergy

Frequent: At least 7% of the general population is affected by manifest contact allergy (eczema) at least once per year, and 15 to 20% are sensitized (allergic) to at least one of the major allergens (and thus at constant risk of relapsing disease any time). The endemic of contact allergy can be explained by the ubiquitous presence of chemicals acting as contact allergens, e.g. preservatives, fragrances, rubber material, metals, which all occur in private (e.g. cosmetics) as well as in occupational settings (e.g. metal workers, construction workers, health care personal).
Severe I
The clinical manifestations of contact allergy can be severe. The following figures may illustrate this:

Contact allergy caused by rubber gloves (Frequently observed in construction workers or health care workers)

…by epoxy resins (e.g. used in the construction of wind mill rotor blades, or in the building trade ). “Airborne contact dermatitis” through vaporisation.

….by hair dyes
Severe II

CONTACT ALLERGY AS AN IMPORTANT THREAT TO HUMAN HEALTH - BEYOND THE MEDICAL PERSPECTIVE

Contact Allergy is a persistent threat to human health: Sensitization, once acquired, cannot be treated.

What does this imply:

1. Usually “ALLERGIES” are considered as being caused by ‘nature’ (plant / food allergens)
   The responsible would be “Le bon Dieu”, the “Good Lord”…

2. In contrast CONTACT ALLERGIES are mainly caused by man-made products. In each case of contact allergy affecting a consumer, there is thus human responsibility.

3. Sensitization is an irreversible change of the immunological memory, comparable to “immunodeficiency” or to a genetic defect caused e.g. by ionizing rays. Both imply a persistent health risk.

4. Consequently, it must be conceived as an interference with individual (personal) integrity, a permanent disability such as a face disfigured by a scar.
   Such interference with personal integrity is at least as problematic as violation of “informational integrity”

5. Where personal integrity is violated, fundamental rights are concerned, no more and no less

6. Are the consumers, the politicians, the manufacturers, even the dermatologists aware of such dimensions of contact allergy?
Prevention through early diagnosis

As contact allergy cannot be cured (see above) it is of utmost importance that the sensitized individual knows “his allergen” enabling him the selection of suitable (allergen-free) products and thus avoiding relapse.

The chemical the individual is sensitized to is identified by the “patch test”. (fig 1 - 3). In patch testing, a chemical suspected to cause contact allergy, e.g. a fragrance or a rubber compound, is applied in minute quantities on the skin.

Fig. 1: A 20 mg petrolatum patch test preparation containing the allergen (e.g.0.2 mg of the fragrance eugenol)

Fig. 2: ….is placed on the back of the patient

Fig. 3: An eczematous reaction after 72 hours indicates an allergy against the substance tested. This is not a "side-effect", but a clear diagnostic outcome.
Diagnosis of contact allergy and the CTD

Thus, the device, a patch preparation containing the chemical and potentially acting as an allergen, is considered as an “allergen”, and according to Directive 2001/83/EC (article 1 (4b) and according to the German Arzneimittelgesetz (AMG) (§4 (5)) are considered as ‘medicinal products’.

It must be considered as a serious neglect that contact allergens such as nickel applied to skin surface are not distinguished from protein allergens such as pollen, which are brought into the skin and thus into the body. Whereas in the former case, there is practically no risk at all for the trial subject, in the latter, serious risks (e.g. anaphylactic shock in the extreme) have to be considered.

This has rather bizarre consequences:

An established cosmetic (or another consumer product) mutates to a medicinal drug

only and only because it is applied as an allergen patch test preparation. There is no increase of risk at all for the study person, which were linked to this particular application method. Only this scenario could be the reason for a different consideration making it a “drug”.

Nevertheless, studies with this preparation have to observe all regulations set out in the CTD:

- preclinical data on the ingredients (e.g. a preservative) with exhaustive toxicological data have to be delivered (although the amount applied is less than 1/100 to 1/1000 compared to a body cream, a deodorant, or whichever type of product is containing the substance in question).

- Insurance amounts to more than 50.000 €, as the number of persons studied reach at least 2,000 to diagnose a minimum of 20 patients. Usually, the sensitization rate in patients routinely tested with newly discovered contact allergens is 1% or less (see publication Annex).

- Certain rules set out in various guidance documents (e.g. obligatory monitoring, notification system for severe drug reactions and many others) are not needed. Side-effects, if ever, are local reactions on the skin (e.g. hyperpigmentation), but no severe
Systemic reactions affecting the whole body have been observed in the hundred years history of patch testing.

- Submission of the request for authorization of a CT is an unnecessary bureaucratic burden in this context.

New patch test preparations which are needed to account for the changing exposure to chemicals in the environment of the consumer and worker have to be tested in accordance with the CTD, and they have to undergo the whole process of marketing authorization.

The requirements resulting from the above directives have to be considered as absolutely prohibitive, to the effect,

**that no clinical trials at all have been conducted with new contact allergen patch test preparations.**

and consequently, no applications for marketing authorization of new contact allergens have been submitted.

**The consequences:**

1. Diagnostic efficacy regarding new allergens is jeopardized, as these are just not available. Individual prevention by selecting the allergen-free product is impossible as the consumer cannot be made aware of “his allergen”.

2. Epidemiologic surveillance of contact allergy is impeded. Neither the manufacturer of products nor the competent authorities of risk assessment and public health surveillance, such as the ‘Bundesinstitut für Risikobewertung’ (BfR) and the ‘Bundesinstitut für Verbraucherschutz und Lebensmittelsicherheit’ (BVL) will be aware of newly arising problems due to allergies.

3. These problems are even aggravated by the fact that epidemiological surveillance of contact allergy, i.e. human observation, will be more crucial in the near future when predictive animal tests aimed at identifying a chemical as an allergen will be prohibited and will be replaced by ‘alternative methods’ (Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products).

In fact, animal tests will be replaced by **experiments in humans** (consumers and workers) *without informed consent* (e.g. “the safety of this product has only been shown in laboratory methods. It is not known if you become sensitized through the product as observational studies are lacking”). Even worse, it is a large-scale experiment conducted in the population *without outcome control*, unique in the world of experimental research.

Although a ‘validation’ process of these alternative methods is required referring to the respective institutions working in these fields (OECD, ECVAM), ‘validation’, mainly an (interlaboratory) comparison of different laboratory methods, is, in fact, internal, and does not include external validation against human observation.

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2 This attitude would be comparable to a manufacturer of aircrafts making take off test planes but who is no longer interested in the course of the flight and safe landing.
observation must be an integral part of the validation process, as it is the indispensable gold standard of any predictive safety assessment, even more, if these are merely "in vitro" predictive tests.

The CTD, by impeding epidemiological surveillance of new contact allergens, makes it impossible for clinicians to try to at least partly compensate for the deficiencies of the EU regulation and EU directive on cosmetics.

**In summary:** The negative impact of the CTD (its intended revision included) on consumers’ and workers’ welfare and health is tremendous.

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**III. Comments on “Revision of the ‘Clinical Trials Directive’ 2001/20/EC. Concept paper submitted for public consultation”**

Although most of the topics raised have no impact on the above problem, some of them shall be commented on:

**I. Cooperation in assessing and following up applications for clinical trials.**

Multinational patch test studies are rare exceptions (one being e.g. the European surveillance system on contact allergies (ESSCA; www.essca-dc.org). Most studies are (were !) national. To cut all the proposed options short, in our view, the best solution would be single submission and only one assessment by one of the competent authorities and one ethic committee of one member state. These could be approved tacitly by other member states. National ethic committees may and probably will want to be involved, but essential amendments putting into question the CT are not to be expected in view of the dimension of the CT (patch test study), and in particular, in view of very rare, and if, mild side effects.

Regarding the consultation item no. 8: Tacit approval would be desirable, but not as ‘CAP’

**II. Better adaptation to practical requirements and a more harmonized risk-adapted approach to the procedural aspects of clinical trials**

The introduction to this paragraph refers to “slightly divergent national provisions”. With regard to patch testing this is a euphemism.

As mentioned, not a single CTD has been conducted with new patch test allergens. This, however, does not mean that no studies with new allergens have been performed. All over Europe, with the exception of Germany, studies are done without observing the mere existence of the CTD, and without interference by the competent authorities. Even more, there is an important manufacturer in Northern Europe offering chemicals to be used as patch test preparation (not authorized!) but indicating correctly: “Not for use in humans”.
Without any doubt there are “divergent national provisions”, to an absurd and unacceptable extent.

Regarding consultation no 9: Answer: Definitely no! Enlarging the definition of ‘non-interventional trials’ could perhaps be an option for the current problem of patch test studies.

**Consultation item no. 10:** agreed.
Consultation item no 11: Agreed in general, but the solutions offered are too hesitant with regard to studies such as patch test studies.

If “more precise and risk adapted rules for the content of the application dossier and for safety reporting” were taken as objective, then, regarding patch testing, no risk adapted rules, no application dossier and no safety reporting (systems) are needed.

Consultation item no 13: agreed in general, but not helpful for the particular problem addressed here.

Consultation item no 14: agreed with either policy options. However, the German AMG requires insurance which must be sufficiently high to cover liability of a maximum of 500,000 € for every study subject. As mentioned, the size of study groups in patch testing must be high (about 2000). Insurance is still an insurmountable and thus prohibitive hurdle.

Consultation item no 15-17: no comments

IV Comments on the “Roadmap”

With reference to:

-Objective no 2: “Regulatory requirements which are adapted to practical requirements, constraints, and needs, without compromising the safety, well-being and rights of clinical trial participants”.

Comment: This objective could be achieved best by excluding totally the patch test studies from the scope of the CTD. The alternative would be to add to the large majority of rules and guidelines the phrase: “not valid/applicable for patch test studies”.

-D. Initial assessment of impacts: the mention of “socio-economic impacts” is welcomed. As mentioned above, one important impact, namely on consumers’ and workers’ welfare and health was not considered at all. Beyond the issue of contact allergy, where the impact has been proven (see above), this question should be addressed more systematically.
V. Conclusions:

If one wants to take an “inductive reasoning” approach, a number of single arguments would necessarily lead up to the conclusion, that over 90% of the CTD is not applicable to patch test studies.

Taking a “deductive” approach governed essentially by sensible reasoning, one must conclude that patch test preparations are not medicinal products, and further amendments of single paragraphs of the CTD would not be needed.

Alternatively and preferably, patch test preparations are considered as medicinal products which need to be authorized, but which have to fulfill only a small set of requirements (e.g. regarding quality control in production), but which do not fall into a study category according to the CTD.

With regard to “safety of trial participants”, the leading issue of the CTD, there is absolutely no reason for concern, considering the long history of patch testing.

The whole problem caused by the CTD and the legislative on drugs (Directive 2001/83/EC (article 1 (4b) and German Arzneimittel Gesetz (AMG) (§4 (5)) regarding the issue exposed here can be explained by one single semantic trap:

The missing distinction between different types of “allergies” and “allergens”.

VI Suggestion

The most practical approach, supported by many studies in the past, would be to go to the “status quo ante”. An example of such studies is included in the Annex (On the “26 EU fragrances”).
VII Stakeholder status

I am a clinical investigator

- Representing the German Contact Dermatitis Research Group (DKG), an association of ~ 90 dermatologists, the Information Network of Departments of Dermatology, a network of over 50 dermatological clinics (IVDK; www.ivdk.org) (in this area the largest network world wide), and the European surveillance system on contact allergy (ESSCA; www.essca-dc.org), a European network of over 30 departments from 11 countries.

- Speaking as a “private individual”, but from a position which is involved in drug safety, consumer safety and workers health protection.

As
- member of the Drug Commission of the German Medical Association (AkdÄ),
- member of the working group “drug safety” of the German BfArM
- member of the ‘Cosmetic commission’ of the BfR (Bundesinstitut für Risikobewertung),
- member of the “MAK Commission” (Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area) of the Deutsche Forschungsgemeinschaft (DFG) and head of its subgroup “Skin and Allergies”

As being involved in questions of drug safety for over 20 years, I highly appreciate the initiative to revise the CTD.

As dermatologist and allergologist I deeply regret the shortcomings of the CTD and that the proposals of the concept paper are still insufficient with regard to the problem outlined.

However, it would be wrong to criticize the CTD and the intended revision in general, as it is only one small but important point to be changed.

Göttingen/Germany 09 May 2011

(Prof Dr. Axel Schnuch
Member of the Board of the DKG
Head of the IVDK)
VIII ANNEX
Sensitization to 26 fragrances to be labelled according to current European regulation

Results of the IVDK and review of the literature

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To study the frequency of sensitization to 26 fragrances to be labelled according to current European regulation. During 4 periods of 6 months, from 1 January 2003 to 31 December 2004, 26 fragrances were patch tested additionally to the standard series in a total of 21,325 patients; the number of patients tested with each of the fragrances ranged from 1,658 to 4,238. Hydroxymethylpentacyclohexene carboxaldehyde (HMPCC) was tested throughout all periods. The following frequencies of sensitization (rates in %, standardized for sex and age) were observed: tree moss (2.4%), HMPCC (2.3), oak moss (2.0), hydroxycitronellal (1.3), isoeugenol (1.1), cinnamic aldehyde (1.0), farnesol (0.9), cinnamic alcohol (0.6), citral (0.6), citronellol (0.5), geraniol (0.4), eugenol (0.4), coumarin (0.4), lilial (0.3), amyl-cinnamic alcohol (0.3), benzyl alcohol (0.3), vinylcinnamate (0.2), benzyl salicylate (0.1), benzyl benzoate (0.1), anisyl alcohol (0.0).

1) Substances with higher sensitization frequencies were characterized by a considerable number of ‘++/++++’ reactions. 2) Substances with low sensitization frequencies were characterized by a high number of doubtful/irritant and a low number of stronger (;++/++++; reactions. 3) There are obviously fragrances among the 26 which are, with regard to contact allergy, of great, others of minor, and some of no importance at all.

Key words: contact allergy; European Union; fragrances; labelling; regulation © Blackwell Munksgaard, 2007.

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Contact allergy (CA) to fragrance compounds is a well-recognized problem. The fragrance mix I (FM I), containing 8 different compounds, ranks second in the statistics of CA for many years (1) and during the 1990s an increase in sensitization frequency caused considerable concern (2). It has been estimated that 2–4% of the general population suffers from CA to fragrances contained in the FM I (3). However, fragrance CA is only partially diagnosed by patch testing with the FM in patients with a history of adverse reactions to fragrances, because further fragrance compounds are capable of causing CA to fragrance products (4–6). At least 2 of them have already been proven to be frequent sensitizers (7–9), namely, farnesol, and hydroxymethylpentacyclohexene carboxaldehyde (HMPCC, Lyral®). This situation prompted the EU to address the issue of prevention. It was decided that, if consumer products contain one or several fragrances out of a list of 26 fragrances considered as contact allergens and compiled by the Scientific Committee on Cosmetics and Non-Food Products (SCCNFP) (http://europa.eu.int/comm/health/ph_risk/committees/sccp/documents/out98_en.pdf), these fragrances should be labelled (10), while the remaining fragrance compounds are still globally labelled as ‘perfume’ as before.

We were interested in the actual frequencies of CA to these 26 fragrance compounds (see Table 2), which were therefore patch tested in consecutive, unselected patients by the IVDK network during a 2-year period.

Methods

The multicentre project IVDK (Information Network of Departments of Dermatology) is an instrument of epidemiological surveillance of CA
and has been described in detail elsewhere (1, 11). Patch tests are performed in accordance with the recommendations of the International Contact Dermatitis Research Group (12) and the German Contact Dermatitis Research Group (DKG) (13). Patch test material is obtained from Hermal/Trolab, Reinbek, Germany. Patch test preparations are applied for 24 or 48 hr. Readings are done until at least 72 hr using the following grading based on international standards (14), further refined by the German Contact Dermatitis Group (13): neg, ?, +, ++, ++++, irritant, follicular. The patch test results of every reading, a standardized history (including age, sex, atopic diseases, current and former occupation(s), presumptive causal exposures), along with final diagnoses and site(s) of dermatitis are assessed and documented. All data are transferred to the data centre in Göttingen in an anonymized format every 6 months.

During 4 periods of 6 months each, from 1 January 2003 to 31 December 2004, 25 fragrances (Table 1) were successively patch tested additionally to the standard series, i.e. in unselected patients, by departments of the IVDK. In the first period 8, in the second 6, in the third 3, and in the last period 8 compounds were added to the standard series, the number of patients tested with each preparation ranging from 1658 (tree moss) to 4238 (farnesol; tested during 2 periods). HMPCC was tested in the standard series in 21 325 patients throughout the study period.

For the description of the demographic characteristics of patients tested the MOAHLFA index is used. MOAHLFA is the acronym for male, occlusional dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, and age >40 (1).

Frequencies of sensitization (as % of patients tested) were calculated both as crude proportions and proportions standardized for sex and age (15). Subgroups of patients defined by sensitization to an index allergen were analysed for concomitant reactions (crude proportions). The reaction index (RI) (16), relating the number of allergic reactions to the number of doubtful or irritant reactions, ranging from RI = −1 (all reactions nonallergic) to RI = +1 (all reactions being allergic), and the positivity ratio (PR), as the proportion (%) of + reactions out of the total number of allergic reactions (17), were calculated as parameters to assess the patch test preparation. A low RI (e.g. −0.8) together with a high PR (e.g. 100%) is indicative of a ‘problematic’ (17) patch test preparation (see Table 2, group III), where a number of the ‘+’ reactions may be suspected to be falsely positive. For data management and analysis, the statistical software package SAS (version 9.1, SAS Institute, Cary, NC, USA) was used.

Results

MOAHLFA index

The population patch tested is described by the relative proportion of the following characteristics (Table 1), which differed slightly between the 4 periods: male (M) 37–39%, occupational dermatitis (O) 14–15%, atopic dermatitis (A) 17–18%, hand dermatitis (H) 26–29%, leg dermatitis (L) 11–15%, face dermatitis (F) 12–16%. The greatest

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Table 1. Demographic description of the test populations of the different test periods using the items of the MOAHLFA index, and substances tested (for number of patients tested see Table 2)

<table>
<thead>
<tr>
<th>Period</th>
<th>I</th>
<th></th>
<th>II</th>
<th></th>
<th>III</th>
<th></th>
<th>IV</th>
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<td>%</td>
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<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Tested</td>
<td>2349</td>
<td>38.2</td>
<td>2170</td>
<td>37.2</td>
<td>2599</td>
<td>38.9</td>
<td>2268</td>
<td>39.1</td>
</tr>
<tr>
<td>M Men</td>
<td>897</td>
<td>38.2</td>
<td>808</td>
<td>37.2</td>
<td>1011</td>
<td>38.9</td>
<td>887</td>
<td>39.1</td>
</tr>
<tr>
<td>O Occupational</td>
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<td>14.9</td>
<td>309</td>
<td>14.2</td>
<td>364</td>
<td>14.0</td>
<td>346</td>
<td>15.3</td>
</tr>
<tr>
<td>A Atopic derma-</td>
<td>432</td>
<td>18.4</td>
<td>368</td>
<td>17.0</td>
<td>457</td>
<td>17.6</td>
<td>391</td>
<td>17.2</td>
</tr>
<tr>
<td>H Hand-derma-</td>
<td>671</td>
<td>28.6</td>
<td>562</td>
<td>25.9</td>
<td>698</td>
<td>26.9</td>
<td>647</td>
<td>28.5</td>
</tr>
<tr>
<td>L Leg-derma-</td>
<td>256</td>
<td>10.9</td>
<td>262</td>
<td>12.1</td>
<td>320</td>
<td>12.3</td>
<td>334</td>
<td>14.7</td>
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<tr>
<td>F Face-derma-</td>
<td>358</td>
<td>15.2</td>
<td>252</td>
<td>11.6</td>
<td>410</td>
<td>15.8</td>
<td>283</td>
<td>12.5</td>
</tr>
<tr>
<td>A &gt;40 years</td>
<td>1505</td>
<td>64.1</td>
<td>1464</td>
<td>67.5</td>
<td>1745</td>
<td>67.1</td>
<td>1605</td>
<td>70.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substances tested during periods</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzy l alcohol, coumarin; citronellol, benzyl salicylate, citral, benzyl cinnamate, α-hexyl-cinnamic aldehyde</td>
<td>Tree moss, lilial, γ-methylionon, αmlyl-cinnamic alcohol, anisyl alcohol, benzyl benzoate,</td>
<td>Linalool, limonene, methylheptin carbonate,</td>
<td>Oak moss abs, isoeugenol, hydroxycitronellal, cinnamic aldehyde, cinnamic alcohol, eugenol, geraniol, α-amyl-cinnamic aldehyde,</td>
<td></td>
</tr>
</tbody>
</table>

HMPCC, hydroxymethylpentylcyclohexene carboxaldehyde.
variation during the study period was observed for 'age 40 and above' (A), namely between 64% and 71%, underscoring the need for standardizing the patch test results to enable comparisons. In contrast, regarding other potentially confounding factors, the patient population can be regarded as sufficiently stable (data not shown).

The MOAHLFA index of groups of patients reacting positive to certain compounds shows that patients reacting to fragrances may differ with regard to some demographic and clinical data: most of the patients were older (higher % of age >40), between 70% and 90%. Only patients reacting to coumarin (38% with age >40), citral (62%) and farnesol (66%) were considerably younger. In citral and coumarin positive patients men were somewhat overrepresented (77% and 63%) and the hands were by far the leading localization of eczema (54% and 75%). This corresponds to a higher percentage of suspected occupational dermatosis (31% and 25%), however, without any hints on specific related occupations or exposures (data not shown). Sensitization to benzyl alcohol, eugenol, geraniol, and cinnamonal was (strongly) associated with leg dermatitis (29%, 46%, 40%, and 33%), indicating an important role of this risk factor, in contrast to low proportions in the case of patients reacting positively to HMPCC (7%), citral (8%), or farnesol (5%). Face dermatitis, which is often caused by cosmetics, was generally increased (>20%) in patients reacting to this group of fragrances, in particular to geraniol (50%), cinnamonal alcohol (39%), and isoeugenol (23%), however, it was not increased in patients with positive reactions to citral, coumarin, eugenol, and benzyl alcohol (15%, 0%, 9%, and 14%, respectively). Finally, the very low number of men reacting to cinnamonal alcohol (8%) is surprising.

**Frequencies of sensitization**

The frequencies of sensitization as expressed by the + to +++ reactions to each of the 26 fragrance compounds are presented in Table 2. The follicular reactions were considered to be non-allergic when calculating the percentages of positive reactions. Leading allergens with the upper confidence interval (CI) > 1.0% are oak moss, tree moss, HMPCC, hydroxyacetone, isoeugenol, cinnamic aldehyde, and farnesol.

A second group of compounds with an upper CI between 1.0% and >0.5% comprises cinnamic alcohol, citral, citronellol, geraniol, eugenol, coumarin, lilial, amyl-cinnamic alcohol, and benzyl cinnamate.

The third group with upper CI of less than 0.5% assembles 10 compounds: benzyl alcohol, linalool, methylheptin carbonate, α-amylyl-cinnamic aldehyde, α-hexyl-cinnamic aldehyde (AHCA), limonene, benzyl salicylate, γ-methylionone, benzyl benzoate (BB), and anisyl alcohol.

Sensitization to allergens of the first group is significantly more frequent than sensitization to allergens of the third group (c.f. CIs not overlapping).

**Sex differences.** The following compounds caused sensitization in women more often than in men: HMPCC (2.7 versus 1.6) and cinnamic alcohol (0.9 versus 0.3), and (nonsignificantly) cinnamic aldehyde (1.2 versus 0.7), and eugenol (0.6 versus 0.2), whereas citral and coumarin appeared to be more frequent in men (1.2 versus 0.3 and 0.7 versus 0.3), respectively.

**Reaction pattern.** Allergens of the first group exhibit a ‘favourable’ reaction pattern with a positive RI (except farnesol) and a low PR (except cinnamic aldehyde), i.e. with a considerable number of stronger (+++/++++) reactions. Allergens of the third group have a negative RI throughout, with more irritant/doubtful than allergic reactions indicating the possibility of false positive reactions. However, stronger allergic reactions (lower PR of benzyl alcohol, limonene, α-amylyl-cinnamic aldehyde) did occur even in this group, indicative of these substances to be – albeit rare – sensitizers.

**Concomitant reactions.** Frequent concomitant reactions (crude rates) in subgroups of patients defined by a sensitization to an index allergen are presented in Table 3. For comparison, the reactions to the FM are disclosed also. With decreasing frequencies of sensitization the number of concomitant reactions increases (Table 3), oak moss and α-amylyl-cinnamic aldehyde being the extremes. Concomitant reactions unrelated to fragrances emerged in a higher frequency also, namely nickel (40% and 33.3%) in farnesol and cinnamic alcohol positives and Lanolin (43%) in benzyl alcohol positives.

**Discussion**

The aim of this study was to evaluate the importance of 26 fragrance compounds qualified as allergens by the EU, with the consequence that they have to be labelled if contained in a product (10), by patch testing consecutive, unselected patients with suspected allergic contact dermatitis with these compounds. The main result of this study is that these compounds are highly heterogeneous with regard to their impact as contact allergens. One group of compounds can undisputedly be regarded as important allergens, namely, our group I (Table 2). Another group of compounds is clearly allergenic but less important in terms of sensitization frequency (group II).
In contrast, a third group comprises 10 compounds which have turned out to be (extremely) rare sensitizers in our analysis, or which in other instances may even be considered as nonsensitizers.

The allergens of group I: Since a long time, oak moss is recognized as an important sensitizer (18–20), particularly confirmed by testing the single constituents in FM I-positive patients (2, 21). In contrast, tree moss is not contained in cosmetic patch test series, and this is the first study in which tree moss was tested in a larger population. With a sensitization prevalence of 2.4% in our patients it turned out to be the most frequent allergen.

Among the >100 constituents identified in oak moss and tree moss (18), atranol and chloroatranol (degradation products of atranorin and chloroatranorin) figure as the most potent allergens (22, 23). The EC3 values in the Local Lymph Node Assay (LLNA) (0.6% and 0.4%) classify them as strong sensitizers (cited in SCCP/0847/04). These substances were found in many perfumes in considerable concentrations (24). In view of the extreme potencies of both substances, which are able to elicit in use tests with concentrations on the ppm level (0.0005%) and in patch testing in the ppb level (0.000015%), the Scientific Committee on Cosmetics (SCCP) came to the conclusion that both substances should not be present at all in cosmetic products (SCCP/0847/04). In a separate data analysis (unpublished) we found that only 53.8% (35/65) tree moss allergic patients reacted to the FM I (containing oak moss), indicating that oak moss alone is probably not suitable for diagnosing tree moss allergy.

Furthermore, tree moss may contain abietic acid and dehydroabietic acid, important allergens of colophony after oxidation. This may explain the high proportion of concomitant reactions to colophony (Table 3). In contrast, oak moss patch test preparations shown to be not contaminated by tree moss or its resins, do not react considerably together with colophony (25, 26).

The notable CA risk associated with exposure to the synthetic fragrance HMPCC has recently gained interest (4, 8, 9, 27–29). In a large European study, 50 out of 1855 consecutive patients (2.7%) tested with a screening series for fragrance allergy had a positive reaction to HMPCC (8).

### Table 2. Results of patch testing 26 fragrances

<table>
<thead>
<tr>
<th>Substance</th>
<th>n test</th>
<th>n pos</th>
<th>% Pos</th>
<th>% Pos std.</th>
<th>95% CI</th>
<th>irr./?</th>
<th>f</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>RI</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tree moss abs 1%</td>
<td>1658</td>
<td>45</td>
<td>2.7</td>
<td>2.4</td>
<td>1.7–3.2</td>
<td>29</td>
<td>4</td>
<td>28</td>
<td>16</td>
<td>1</td>
<td>0.2</td>
<td>62.2</td>
</tr>
<tr>
<td>HMPCC 5%</td>
<td>21325</td>
<td>502</td>
<td>2.4</td>
<td>2.3</td>
<td>2.1–2.6</td>
<td>149</td>
<td>19</td>
<td>361</td>
<td>116</td>
<td>25</td>
<td>0.5</td>
<td>71.9</td>
</tr>
<tr>
<td>Oak moss abs. 1%</td>
<td>2063</td>
<td>46</td>
<td>2.2</td>
<td>2.0</td>
<td>1.4–2.6</td>
<td>18</td>
<td>3</td>
<td>29</td>
<td>14</td>
<td>3</td>
<td>0.4</td>
<td>63.0</td>
</tr>
<tr>
<td>Hydroxycteroninal 1%</td>
<td>2063</td>
<td>27</td>
<td>1.3</td>
<td>1.3</td>
<td>0.7–1.8</td>
<td>9</td>
<td>0</td>
<td>20</td>
<td>6</td>
<td>1</td>
<td>0.5</td>
<td>74.1</td>
</tr>
<tr>
<td>Isoeugenol 1%</td>
<td>2063</td>
<td>26</td>
<td>1.3</td>
<td>1.1</td>
<td>0.7–1.6</td>
<td>17</td>
<td>2</td>
<td>19</td>
<td>7</td>
<td>0</td>
<td>0.2</td>
<td>73.1</td>
</tr>
<tr>
<td>Cinnaminaldehyde 1%</td>
<td>2063</td>
<td>21</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5–1.5</td>
<td>15</td>
<td>1</td>
<td>19</td>
<td>1</td>
<td>1</td>
<td>0.1</td>
<td>90.5</td>
</tr>
<tr>
<td>Farnesol 5%</td>
<td>4238</td>
<td>38</td>
<td>0.9</td>
<td>0.9</td>
<td>0.6–1.2</td>
<td>38</td>
<td>6</td>
<td>30</td>
<td>7</td>
<td>1</td>
<td>−0.1</td>
<td>78.9</td>
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<tr>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cinnamalcohol 1%</td>
<td>2063</td>
<td>13</td>
<td>0.6</td>
<td>0.6</td>
<td>0.2–1.0</td>
<td>14</td>
<td>0</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0.0</td>
<td>92.3</td>
</tr>
<tr>
<td>Citral 2%</td>
<td>2021</td>
<td>13</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3–1.0</td>
<td>11</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Citronellol 1%</td>
<td>2003</td>
<td>9</td>
<td>0.4</td>
<td>0.5</td>
<td>0.1–0.8</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0.1</td>
<td>88.9</td>
</tr>
<tr>
<td>Geraniol 1%</td>
<td>2063</td>
<td>10</td>
<td>0.5</td>
<td>0.4</td>
<td>0.1–0.7</td>
<td>18</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>−0.3</td>
<td>80.0</td>
</tr>
<tr>
<td>Eugenol 1%</td>
<td>2065</td>
<td>11</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2–0.7</td>
<td>11</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>−0.1</td>
<td>81.8</td>
</tr>
<tr>
<td>Coumarin 5%</td>
<td>2020</td>
<td>8</td>
<td>0.4</td>
<td>0.4</td>
<td>0.1–0.8</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0.1</td>
<td>87.5</td>
</tr>
<tr>
<td>Lilial 10%</td>
<td>2004</td>
<td>8</td>
<td>0.4</td>
<td>0.4</td>
<td>0.1–0.6</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0.3</td>
<td>75.0</td>
</tr>
<tr>
<td>Amyl-cinnaminalcohol 1%</td>
<td>1977</td>
<td>7</td>
<td>0.4</td>
<td>0.3</td>
<td>0.1–0.6</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>−0.1</td>
<td>85.7</td>
</tr>
<tr>
<td>Benzyl cinnamate 5%</td>
<td>2042</td>
<td>6</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1–0.6</td>
<td>7</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>−0.1</td>
<td>66.7</td>
</tr>
<tr>
<td><strong>Group III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Benzyl alcohol 1%</td>
<td>2166</td>
<td>7</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1–0.5</td>
<td>12</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>−0.3</td>
<td>42.9</td>
</tr>
<tr>
<td>Linalool (stab.) 10%</td>
<td>2401</td>
<td>7</td>
<td>0.3</td>
<td>0.2</td>
<td>0.0–0.4</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>−0.3</td>
<td>85.7</td>
</tr>
<tr>
<td>Methylheptin carbonate 1%</td>
<td>2401</td>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0–0.4</td>
<td>12</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>−0.3</td>
<td>83.3</td>
</tr>
<tr>
<td>α-Amyl-cinnamic aldehyde 1%</td>
<td>2062</td>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
<td>0.0–0.3</td>
<td>13</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>−0.6</td>
<td>75.0</td>
</tr>
<tr>
<td>α-Hexyl-cinnamic aldehyde 10%</td>
<td>2019</td>
<td>3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0–0.3</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>−0.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Limonene 2%</td>
<td>2396</td>
<td>3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0–0.3</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>−0.4</td>
<td>66.7</td>
</tr>
<tr>
<td>Benzyl salicylate 1%</td>
<td>2041</td>
<td>2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0–0.2</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>−0.6</td>
<td>100.0</td>
</tr>
<tr>
<td>γ-Methylionon 1%</td>
<td>2004</td>
<td>1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0–0.2</td>
<td>11</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>−0.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Benzyl benzoate 1%</td>
<td>2003</td>
<td>1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0–0.1</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>−0.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Anisyl alcohol 1%</td>
<td>2004</td>
<td>1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0–0.1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>−0.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HMPCC, hydroxymethylpentylcyclohexene carboxaldehyde. Number of patients tested (n); number and proportion of patients reacting allergic (n pos/% pos), frequency of allergic reactions, standardized for age and sex (% Pos. std; column 5), together with the 95% confidence interval (95% CI; column 5) and reaction pattern of the patch test preparations (irr: irritant; f: follicular; ?: doubtful; RI: reaction index; PR: positivity ratio).
In only 60% of these HMPCC-hypersensitive individuals, there was a simultaneous CA to the FM (8). HMPCC was tested by the DKG in 3245 consecutive patients of which 62 (1.9%) had positive reactions (9). A group of European dermatologists developed a mix of 6 fragrances (FM II), including HMPCC, to be tested in consecutive patients (28). In this study, 2.9% reacted to the medium concentration (14%) of this mix, and >1/3 were shown to be allergic to its compound HMPCC, making it the dominating allergen of the FM II (28). In view of a sensitization frequency of 2.3% observed in our study, HMPCC must be regarded as one of the most important single fragrance allergens. In addition to the evident impact of HMPCC derived from clinical epidemiology, a use test (repeated open application test, ROAT) with 2 different concentrations (0.5% and, if negative, 3% with ethanol as vehicle) was conducted in 18 patients allergic to HMPCC as diagnosed by prior patch testing (29). In 16 of 18 cases (89%) a positive use test developed, 11 reacting to the low and 5 only to the high concentration.

Isoeugenol was, for a long time, the second most important fragrance allergen of the FM I (19, 21, 30). According to our data hydroxycitronellal (1.3% positive, Table 2), although less potent but probably more often used, is an allergen as important as isoeugenol (1.1%). Marked concomitant reactivity may be explained by the presence of isoeugenol in balsam of Peru or coexposure together with oak moss (Table 3). According to human and animal predictive tests isoeugenol is classified as a sensitizer of moderate potency (Human class 2, LLNA EC 3 of 1.3%) (31, 32). The biochemical mechanism of sensitization through isoeugenol may rely on the formation of an orthoquinone, whereas eugenol may react via a phenolic radical mechanism, explaining the relative rarity of concomitant reactions between the 2 substances (33) (Table 3). Interestingly, cases of sensitization in Japanese populations seem significantly less frequent than in Caucasian populations (34). Quantitative aspects of isoeugenol CA were assessed by use and patch tests (35–37).

Hydroxycitronellal is a fragrance widely used in perfumes and products of daily life (38, 39), and, if contained in higher concentrations, capable of causing CA (40). In experimental sensitization tests it was shown to be a weak to moderate

<table>
<thead>
<tr>
<th>Allergen</th>
<th>n pos</th>
<th>FM</th>
<th>Frequent concomitant reactions [% of those reacting positively to the index allergen (left column)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oak moss</td>
<td>46</td>
<td>80.0</td>
<td>None</td>
</tr>
<tr>
<td>Tree moss</td>
<td>45</td>
<td>57.1</td>
<td>Colophony, Oak moss, Hydroxycitronellal, Balsam of Peru</td>
</tr>
<tr>
<td>HMPCC (Lyral®)</td>
<td>502</td>
<td>50.7</td>
<td>Oak moss, Hydroxycitronellal, Balsam of Peru</td>
</tr>
<tr>
<td>Isoeugenol</td>
<td>26</td>
<td>83.3</td>
<td>Oak moss, Balsam of Peru</td>
</tr>
<tr>
<td>Hydroxycitronellal</td>
<td>27</td>
<td>66.7</td>
<td>Oak moss, Balsam of Peru</td>
</tr>
<tr>
<td>Farnesol</td>
<td>22</td>
<td>25.0</td>
<td>Nickel, Cinnamic alcohol, Balsam of Peru</td>
</tr>
<tr>
<td>Cinnamic aldehyde</td>
<td>21</td>
<td>70.0</td>
<td>Cinnamic aldehyde, Balsam of Peru</td>
</tr>
<tr>
<td>Cinnamic alcohol</td>
<td>13</td>
<td>91.7</td>
<td>Balsam of Peru</td>
</tr>
<tr>
<td>Citral</td>
<td>13</td>
<td>76.9</td>
<td>Geraniol, HMPCC, Citronellol, Balsam of Peru</td>
</tr>
<tr>
<td>Eugenol</td>
<td>11</td>
<td>80.0</td>
<td>Balsam of Peru, Oak moss</td>
</tr>
<tr>
<td>Geraniol</td>
<td>10</td>
<td>66.7</td>
<td>Cinnamic aldehyde, Isoeugenol, Cinnamic aldehyde</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>7</td>
<td>28.6</td>
<td>Hydroxycitronellal, Balsam of Peru</td>
</tr>
<tr>
<td>α-Amyl-cinnamic aldehyde</td>
<td>4</td>
<td>75.0</td>
<td>All substances of the FM</td>
</tr>
</tbody>
</table>

HMPCC, hydroxymethylpentylecyclohexene carboxaldehyde; FM, fragrance mix.

*a* Separate analysis of IVDK-data (unpublished) on 65 tree moss positives.
sensitizer (18, 41), with an EC3 value of 20% (31), and a weak experimental elicitor (42). In a Human Repeated Insult Patch Test it was shown that humans can be sensitized by 5% and that challenge with concentrations as low as 1% can elicit reactions (41). Reviewing the literature, the Research Institute on Fragrance Materials (RIFM) expert panel concluded that 1% hydroxycitronellal is not likely to induce sensitization in humans with repeated exposure (43). If applied in the course of a ROAT in the area of former exposure and eczema (axillae), very low concentrations (0.032–0.32%) were sufficient to elicit reactions (44). In contrast, in an experimental model (hand immersion study) simulating real life exposure to diluted dish washing liquids containing the fragrance in higher concentrations (250 ppm), the development of visible eczema was not increased in sensitized subjects (45), although the combined exposure to an allergen and a detergent may enhance the allergic (patch test) reaction (46).

Testing with 4% yielded 13.8% allergic reactions (34), a very high rate caused by the selection of patients, and additionally by the high patch test concentration. Frosch et al. (27) used patch test concentrations of 1% in pet., which resulted in a lower frequency of 0.75% allergic reactions. In our study, hydroxycitronellal turned out to be an important sensitizer, with 1.3% allergic reactions, of which a considerable number were strong (+++), expressed by a low PR (Table 2). A relatively high rate of concomitant reactions to oak moss and HMPCC is very probably due to coexposure in cosmetics.

In numerous experimental studies (with and without adjuvant) in animals and humans the skin sensitizing properties of cinnamic aldehyde (cinnamal) have been demonstrated (47). Sensitization in humans was induced by concentrations in the range of 0.5–1% (48, 49). The EC3 values derived from the LLNA range from 1.4% and 3.1%, classifying the substance as a moderate to strong sensitizer (32, 50, 51). In an exposure-based risk assessment it was shown that the use of 1000 ppm (0.1%) in a leave-on cosmetic would pose an unacceptably high risk of sensitization, whereas the same concentration in a shampoo would pose an acceptable risk (52). In a ROAT it has been shown that deodorants containing cinnamic aldehyde can elicit axillary eczema in sensitized individuals, with concentrations ranging from 0.01% (1 reacting) to 0.1%, the majority reacting to 0.032% (53), complementing former results where 8/22 individuals reacted to 0.1% (54). In a larger European study in unselected patients cinnamic aldehyde was one of the more frequently diagnosed contact allergens (0.9%) (27), which is in line with the frequency found in our study (1.0%). A higher frequency was found in a North American study (1.7%) which can probably be explained by preselection of patients (55). In different test periods 10%, 13%, and 20% of FM I-positive patients reacted to cinnamic aldehyde (21, 30, 56), also reflecting the decreasing sensitization to cinnamic aldehyde (19, 57), which is probably due to a restricted use of this fragrance (58).

Cinnamic aldehyde is partly transformed into cinnamic alcohol and mainly to cinnamic acid, whereas the transformation of cinnamic alcohol to the aldehyde is minimal (59, 60). Concomitant reactions between alcohol and aldehyde (Table 3) may therefore be due to metabolism, cross-reactions, and coexposure, but isolated reactions to either compounds do occur quite often (~ 50%) (61).

Farnesol, a fragrance with some antimicrobial activity (62), is often used in deodorants, exploiting this very additional property. The first larger patch test study with 5% and 10% in petrolatum (pet.) was done in 1985 in Japan. The suitable concentration was found to be 10%, and the proportion of positive reactions was 1.1% (63). In 2 European multicentre studies 1855 and 1703 consecutive patients were patch tested with farnesol (5% in pet) (4, 28). 0.5% and 0.35% reacted allergic, but the number of doubtful reactions was high (1.1% and 1.76%). With a frequency of 0.9% (CI: 0.6–1.2), 30 + and 8 +/+ reactions in our study (Table 2) and with results from a 20-year-old study reporting again 1.1% positive reactions (64) together with several case reports (65–67) there is no doubt that farnesol must be considered an important sensitizer, although its potency was classified as only weak (68) to moderate (69) in animal experiments.

The distinct pattern of low frequencies of cosensitizations with other fragrances, but a surprisingly high association with nickel (Table 3), may be cautiously interpreted as a hint on more specific exposure pathways to this fragrance. The fact that female clerks of younger age (7) and nickel sensitization were somehow overrepresented in farnesol-positive patients may give rise to further thoughts on a social class-specific consumer behaviour, having in mind, that nickel-allergy could be regarded as a ‘socially guided allergy’ (70).

The allergens of group II according to our list (see Table 2), although frequently used (38, 39, 71–73), are clearly less important with regard to frequency of sensitization – partly (in contrast to our results) with no reactions at all in a number of previous studies (4, 27, 28, 34, 63, 64, 74–76) – as well as limited sensitizing potency (18, 31, 32, 49,
77, 78). However, the reaction profiles (RI and PR) indicate that a few unequivocal (stronger) allergic reactions did occur, leaving no doubt that these compounds do have sensitizing properties.

In this group, the ‘unusual’ characteristics of those patients sensitized to citral and coumarin stand out. In both subgroups, men prevailed, and occupational dermatoses was more often suspected, going along with the hands as most commonly affected anatomical site. As this pattern had been noted before, it was suggested to include coumarin and citral in a special ‘hand eczema series’ (79).

Interestingly, concomitant reactions between citral and geraniol occurred frequently (83%; Table 3). This may be due to coexposure, but probably also to cross-reactions, as both compounds are structurally closely related. In larger European studies, citral ranked third and second among several fragrances (4, 28). In a selected group of patients with hand eczema, who were tested with 14 fragrances found in household products, citral was found to be an important allergen (28/658; 4.3%) (79). In a second study the authors further analysed the patients reacting to citral (80). Beside the 28 positive cases, there were 82 cases with irritant patch test reactions, showing citral as an allergen and an irritant, at least under patch test conditions.

In contrast to our results and a former study (4), no cases of coumarin allergy were observed in a recent study (28). Kunkeler et al. (81) reviewed all the cases tested in their department in Amsterdam between 1978 and 1997 (n ~ 14 000). They identified 58 patients with at least a + reaction (0.4%). Given the missing sensitization to coumarin in predictive tests, the authors speculate that the coumarin positive cases may be sensitized by (alkyl-substituted) coumarin derivatives.

**Compounds of group III** (Table 2) can be regarded as very rare allergens or apparently turn into allergens only after substantial oxidation (e.g. limonene and linalool) (82). In the case of some compounds the alleged sensitizing properties can even be doubted, considering the possibility of false positive reactions in view of mainly doubtful or irritant reactions (see RI and PR Table 2). Even if there may indeed be single cases of CA to these compounds reported in the world literature, these may be more indicative of an increased individual susceptibility, than of the substance-specific sensitizing properties, as in the case of highly purified white pet. Ph. Eur. (83). One example may be AHCA, with one unequivocal case of CA to AHCA, displaying multiple sensitization to other fragrances seen by one of the authors (A.S.). Although the substance is used as a positive control, as a calibrant for comparing the consistency of LLNA responses (84), the number of documented allergic cases in humans is very low. We observed 3+ and 11 irritant reactions (Table 2).

In a recently published European study on 1701 consecutive patients, 2 allergic and 16 doubtful reactions to 10% AHCA were reported (28).

Doubts are even more justified with regard to the ‘allergen’ BB. It was shown to be a ‘weak sensitizer’ (69), and rare cases had been observed (85–89). However, in view of its frequent use as an acaricide with 25% concentration (90), and the virtual lack of allergic reactions to this topical drug, it seems not plausible to regard BB as a ‘significant contact allergen’ (91).

**Conclusion**

This study emphasizes again the need for a ‘differentiated look’ on fragrances as contact allergens (21). The 26 fragrances were allocated to 3 different classes according to their importance in terms of frequency of sensitization, only. Nevertheless, a differentiated evaluation of compounds of each class may be needed for overall evaluation, considering not only frequency of sensitization, but also the amount of exposure or use, as well as allergenic potency, eventually together with the real extent of exposure to (highly) oxidized materials. For some substances regulation in terms of use concentration restriction, labelling, or even ban is needed (group I), for others labelling alone may be an adequate instrument of secondary prevention (group II). For *at least some* of the group III compounds neither restrictions nor labelling seems justified. Based on very low frequencies of sensitization despite a widespread use and (very) low potencies in predictive tests, these are probably not significant allergens at all. Further studies in other European countries on large test populations like ours should be performed as there might be regional differences in sensitization. The decision of the EU on labelling 26 compounds (because they were considered as allergens) should be revised. Some manufacturers of cosmetics have decided to use none of the ‘26 annex compounds’ but other compounds instead which do not need to be labelled. However, these alternative fragrance compounds may be less well studied from a toxicological point of view, and as they are mostly unknown to dermatologists, they are not patch tested, and possible CA remains undetected. In summary, prudent labelling must take into account both the risk profile of the respective compound, and subsequent replacement policies of manufacturers which may, in turn, have serious implications for consumer safety.
References

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